Klinefelter Syndrome

BY

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Synonyms

- Klinefelter syndrome
- Klinefelter's syndrome
- XXY male / syndrome
- XXXY syndrome
- XXYY syndrome
- XXXXY syndrome
- XXXYY syndrome

Historical Background

- In **1942**, **Klinefelter** et al published a report on **9 men** who had
  - enlarged breasts,
  - sparse facial and body hair,
  - small testes, and
  - an inability to produce sperm.
- In **1959**, these men with Klinefelter syndrome were discovered to have an **extra sex chromosome (genotype XXY)** instead of the usual male sex complement (genotype XY).

Definition

- It is defined classically by a 47,XXY karyotype with variants that demonstrate additional X and Y chromosomes.
- The syndrome is characterized by
  - hypogonadism (small testes, azoospermia, oligospermia),
  - gynecomastia in late puberty,
  - psychosocial problems,
  - hyalinization and fibrosis of the seminiferous tubules, and
  - elevated urinary gonadotropin levels

Incidence

- Klinefelter syndrome is the **most common chromosomal disorder associated with male hypogonadism and infertility**.

Pathophysiology

(1) The addition of more than one extra X or Y chromosome to a male karyotype results in variable physical and cognitive abnormalities

- The **X chromosome** carries genes that play roles in many body systems, including testis function, brain development, and growth)

- *In general, the extent of phenotypic abnormalities, including **mental retardation**, is directly related to the number of supernumerary X chromosomes. As the number of X chromosomes increases, somatic and cognitive development are more likely to be affected.*

Pathophysiology

- ***Skeletal and cardiovascular abnormalities*** *can become increasingly severe.*
- ***Gonadal development*** *is particularly susceptible to each additional X chromosome, resulting in seminiferous tubule dysgenesis and infertility, as well as hypoplastic and malformed genitalia in polysomy X males.*
- *Moreover,* ***mental capacity diminishes*** *with additional X chromosomes. The intelligence quotient (****IQ****) score is reduced by approximately* ***15 points for each supernumerary X chromosome****, but conclusions about reduced mental capacity must be drawn cautiously.*

Pathophysiology

- All major areas of development, including expressive and receptive language and coordination, are affected by extra X chromosome material.
- The major consequences of the extra sex chromosome, usually acquired through an error of **non-disjunction** during parental gametogenesis, include
  1. **Hypogonadism**
  2. **Gynecomastia**
  3. **Psychosocial problems**.

Pathophysiology

(2) Klinefelter syndrome is a form of primary testicular failure, with elevated gonadotropin levels due to lack of feedback inhibition by the pituitary gland. **Androgen deficiency** causes:

- eunuchoid body proportions;
- sparse or absent facial, axillary, pubic, or body hair;
- decreased muscle mass and strength;
- feminine distribution of adipose tissue;
- gynecomastia;
- small testes and penis;
- diminished libido;
- decreased physical endurance; and
- osteoporosis.

Pathophysiology

(3) The loss of functional seminiferous tubules and Sertoli cells results in a marked decrease in inhibin B levels, which is presumably the hormone regulator of the follicle-stimulating hormone (FSH) level. The hypothalamic-pituitary-gonadal axis is altered in pubertal patients with Klinefelter syndrome.

Pathophysiology

(4) Increased incidence of autoimmune disorders, such as SLE, RA and Sjogren syndrome, has been reported. This may be due to lower testosterone and higher estrogen levels, since androgen may protect against (and estrogen promotes) autoimmunity.

Frequency (United States)

- Klinefelter syndrome is the **most common genetic form of male hypogonadism**.
- Approximately **1 in 500-1,000** males is born with an extra sex chromosome; more than 3,000 affected males are born yearly.
- The prevalence rate is **5-20 times higher** in individuals with **mental retardation** than in the general newborn population.
- Approximately **250,000** men in the United States have Klinefelter syndrome.

Mortality/Morbidity

- About **40%** of concepti with Klinefelter syndrome survive the fetal period.
- In general,
  - the **severity** **of somatic malformations** in Klinefelter syndrome is proportional to the **number of additional X chromosomes**;
  - **mental retardation** and **hypogonadism** are more severe in patients with **49,XXXXY** than in those with 48,XXXY.
- The ***mortality rate*** is ***not significantly higher*** than in healthy individuals.

Epidemiology

- **Race** Klinefelter syndrome **does not have any racial predilection**.
- **Sex** Because the syndrome is caused by an additional X chromosome on an XY background, this condition affects **only males**.
- **Age** Klinefelter syndrome goes undiagnosed in most affected males; among males with known Klinefelter syndrome, many do not receive the **diagnosis** until they are **adults**. The most common indications for karyotyping are **hypogonadism** and **infertility**.

Clinical

(A) History

- ***Infertility*** and ***gynecomastia*** are the 2 most common symptoms that lead to diagnosis in patients with Klinefelter syndrome.
- **Other symptoms include:**
  - fatigue, weakness,
  - osteoporosis,
  - erectile dysfunction,
  - subnormal libido,
  - language impairment, academic difficulty,
  - poor self-esteem, and
  - behavioral problems

Clinical

(B) Clinical ex.

Growth

Infants and children achieve normal height, weight, and head circumference. About 25% have clinodactyly.

Height velocity increases by age 5 years, and **adults** with Klinefelter syndrome are usually **taller** than adults who do not have the syndrome. Affected individuals also have **disproportionately long arms and legs**. Some individuals with Klinefelter variant 49,XXXXY have short stature.

A Child with Klinefelter syndrome. Other than a thin build and disproportionately long arms and legs, the phenotype is normal.

Clinical

(B) Clinical ex.

CNS

- Contrary to other genetic syndromes that arise from chromosomal trisomy (eg, Down syndrome, trisomy 18), the general cognitive ability of patients with Klinefelter syndrome is not typically in the intellectual disability range.
- Most males with the 47,XXY karyotype have normal intelligence. Family background influences intelligence quotient (IQ) score. Subnormal intelligence or mental retardation may be associated with the presence of a higher number of X chromosomes.

Clinical

(B) Clinical ex.

CNS

- About 70% of patients have minor developmental and learning disabilities. These may include academic difficulties, delayed speech and language acquisition, diminished short-term memory, decreased data-retrieval skills, reading difficulties, dyslexia, and attention deficit disorder.
- Patients may exhibit behavioral problems and psychological distress. This may be due to poor self-esteem and psychosocial development or a decreased ability to deal with stress.
- Psychiatric disorders involving anxiety, depression, neurosis, and psychosis are more common in this group than in the general population.

Clinical

(B) Clinical ex.

Dental

- About **40%** of patients have **taurodontism**, which is characterized by enlargement of the molar teeth by an extension of the pulp. The incidence rate is about **1%** in **healthy XY individuals**.

Clinical

(B) Clinical ex.

Sexual characteristics

1. Patients may **lack secondary sexual characteristics** because of a ***decrease in androgen production***. This results in →
   - sparse facial, body, or sexual hair;
   - a high-pitched voice; and
   - fat distribution as is observed in females

Clinical

(B) Clinical ex.

Sexual characteristics

2. By late puberty, 30-50% of boys with Klinefelter syndrome present with **gynecomastia**, which is secondary to ***elevated estradiol levels*** and ***increased estradiol-to-testosterone ratio***

- The risk of developing ***breast carcinoma*** is at least **20 times higher** than in healthy individuals.

Clinical

(B) Clinical ex.

Sexual characteristics

3. Postpubertal patients may have **testicular dysgenesis** (small firm testis; testis size, <10 mL).

4. **Infertility, azoospermia, or both** may result from atrophy of the seminiferous tubules.

- Practically all individuals with a 47,XXY karyotype are infertile.
- Patients with Klinefelter syndrome mosaicism (46,XY/47,XXY) can be fertile.

Clinical

(B) Clinical ex.

Sexual characteristics

5. Patients may have an increased frequency of extragonadal germ cell tumors such as embryonal carcinoma, teratoma, and primary mediastinal germ cell tumor.

Adolescent male with gynecomastia and Klinefelter syndrome.

Adolescent male with Klinefelter syndrome who has female-type distribution of pubic hair and testicular dysgenesis.

Clinical

(B) Clinical ex.

Cardiac & circulatory problems

- **Mitral valve prolapse** occurs in 55% of patients.
- **Varicose veins** occur in 20-40% of patients.
- The prevalence of **venous ulcers** is 10-20 times higher than in healthy individuals, and the risk of **deep vein thrombosis** and **pulmonary embolism** is increased.

Klinefelter Variants

48,XXYY variant: Patients typically have

- **mild mental retardation**
- tall stature
- eunuchoid body habitus
- sparse body hair
- gynecomastia
- long, thin legs
- hypergonadotropic hypogonadism
- small testes

Klinefelter Variants

48,XXXY variant: Patients typically have

- mild-to-moderate mental retardation,
- speech delay,
- slow motor development,
- poor coordination,
- **immature behavior**,
- normal or tall stature,
- abnormal face (epicanthal folds, hypertelorism, protruding lips),
- hypogonadism,
- gynecomastia (33-50%),
- hypoplastic penis,
- infertility,
- clinodactyly
- radioulnar synostosis and benefit from testosterone therapy

Klinefelter Variants

49,XXXYY: Patients typically have

- **moderate-to-severe mental retardation,**
- passive but **occasionally aggressive** behavior and temper tantrums,
- tall stature,
- dysmorphic facial features,
- gynecomastia, and
- hypogonadism

Klinefelter Variants

49,XXXXY variant:

The classic **triad** is

- mild-to-moderate mental retardation,
- radioulnar synostosis, and
- hypergonadotropic hypogonadism.

Other clinical features include

- **severely impaired language**,
- **short stature in some individuals**,
- behavioral problems, low birthweight,
- abnormal face (round face in infancy, coarse features in older age, hypertelorism, epicanthal folds, prognathism),
- short or broad neck, gynecomastia (rare), congenital heart defects (patent ductus arteriosus is most common), skeletal anomalies (genu valgus, pes cavus, fifth finger clinodactyly), muscular hypotonia,
- hyperextensible joints, hypoplastic genitalia cryptorchidism

Causes

Presence of additional X chromosome in a male

50-60% of cases are due to maternal non-disjunction (the remaining cases are due to paternal non-disjunction)

The **most common karyotype** is **47,XXY**, which accounts for **80-90%** of all cases. **Mosaicism** (46,XY/47,XXY) is observed in about **10%** of cases. **Other** variant karyotypes, including 48,XXYY; 48,XXXY; 49,XXXYY; and 49,XXXXY, are **rare**.

D.D.

- ***Hypogonadism***
- ***Marfan Syndrome***

Other Problems to Be Considered

- ***Kallmann syndrome***
- ***46,XX*** karyotype (in ***males***)
- Infertility

Workup

(A) Laboratory Studies

Cytogenetic studies

- The 47,XXY variant is found in 80-90% of patients.
- About 10% of patients have mosaicism; karyotypes include 46,XY/47,XXY; 46,XY/48,XXXY; and 47,XXY/48,XXXY.
- Remaining cases include variants such as the 48,XXYY; 48,XXXY; 49,XXXYY; and 49,XXXXY karyotypes.
- About 1% of cases are due to a structurally abnormal X in addition to a normal X and Y, such as 47,X,i(Xq)Y and 47,X,del(X)Y.

47,XXY karyotype

Workup

(A) Laboratory Studies

Hormone testing

- Patients aged **12-14 years** have **high** plasma **FSH, LH, and estradiol** levels and **low** plasma **testosterone** levels.
- In **response** to administration of human chorionic gonadotropin (**hCG**), the increase in testosterone levels in patients with Klinefelter syndrome is **diminished** compared with the general population.

Workup

(A) Laboratory Studies

Hormone testing

- **Urinary gonadotropin** levels are increased because of abnormal Leydig cell function.

- Serum **osteocalcin** levels are decreased and the hydroxyl-proline–to-creatinine ratio is increased, reflecting decreased bone formation and increased bone resorption.

Workup

(A) Laboratory Studies

Imaging studies

- ***Echocardiography*** is performed to assess for mitral valve prolapse.

- ***Radiography*** is performed to assess for lower bone mineral density, radioulnar synostosis, and taurodontism.

Workup

(A) Laboratory Studies

Histological Findings

- *Histologic findings may include small, firm testes with seminiferous tubular hyalinization; sclerosis; and atrophy with focal hyperplasia of mostly degenerated Leydig cells. Germ cells are markedly deficient or absent. Spermatogenesis is rare.*

Workup

(A) Laboratory Studies

Histological Findings

- *In patients with mosaicism, progressive degeneration and hyalinization of seminiferous tubules take place after puberty despite the presence of normal-sized testes and spermatogenesis at puberty.*

- *Histology of gynecomastic breasts reveals hyperplasia of interductal tissue.*

Treatment

Medical Care

- *Early identification and anticipatory guidance are extremely helpful, although Klinefelter syndrome is rarely diagnosed in prepubertal males.*
- *Treatment should address 3 major facets of the disease:*
  1. *hypogonadism,*
  2. *gynecomastia, and*
  3. *psychosocial problems*

Treatment

Medical Care

Androgen therapy

- *Androgen therapy is the most **important** **aspect of treatment**. Testosterone replacement should **begin at puberty** to correct androgen deficiency, to provide appropriate virilization, and to improve psychosocial status.*
- ***Regular testosterone injections can promote** strength and facial hair growth; build a more muscular body type; increase sexual desire; enlarge the testes; improve mood, self-image, and behavior; and protect against precocious osteoporosis.*

Treatment

Medical Care

Genetic counseling

- *The recurrence risk is not increased above that in the general population.*

- *Physicians should provide parents with information from unbiased follow-up studies of children with Klinefelter syndrome.*

- *The best time to reveal the condition to an affected male is probably mid-to-late adolescence, when he is old enough to understand his condition.*

Treatment

Surgical Care

- ***Mastectomy*** *may be indicated for gynecomastia, which places considerable psychological strain on the patient and increases the risk of breast cancer.*

Consultations

- *Consultations may include the following:*
  - *Clinical geneticist*
  - *Endocrinologist*
  - *Surgeon*
  - *Psychologist*
  - *Speech therapist*

Treatment

Surgical Care

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Treatment

Surgical Care

- ***Mastectomy*** *may be indicated for gynecomastia, which places considerable psychological strain on the patient and increases the risk of breast cancer.*

Consultations

- *Consultations may include the following:*
  - *Clinical geneticist, Endocrinologist, Surgeon, Psychologist and Speech therapist*

Diet *No special diet is needed.*

Activity *No activity restrictions are required.*

Treatment

Androgen

Exogenous androgen (testosterone) is the treatment of choice for many aspects of Klinefelter syndrome.

- ***Drug name:*** *Testosterone enanthate (Delatestryl) or cypionate (Depo-Testosterone)*
- ***Major therapeutic aims*** *are to reduce serum gonadotropin concentrations to the upper limits of normal and to gradually induce virilization.*

Treatment

Androgen

- ***Adult dose:*** *200 mg IM q2-3wk*
- ***Pediatric dose:*** *Beginning at age 11-12 years: 50 mg IM every month (qmo); increase dosage annually in accord with the patient's state of well-being, degree of virilization, growth, and serum gonadotropin levels, eventually reaching adult dose*
- ***Interactions:*** *increases effects of warfarin; increases propranolol clearance*

Treatment

Androgen

- ***Contraindications:*** *Documented hypersensitivity; severe renal, hepatic, or cardiac disease; prostate or breast cancer in males; hypercalcemia*
- ***Pregnancy:*** *X - Contraindicated; benefit does not outweigh risk*

Treatment

Androgen

- ***Precautions / adverse effects:*** *Initiation of therapy may be associated with* ***priapism*** *(rare);* ***other adverse effects*** *include salt and water retention with edema and hypertension, polycythemia, and transient or increased gynecomastia; large doses in older patients may produce prostatic hypertrophy, leading to acute bladder outlet obstruction*

Follow-up

- Further Inpatient Care: Admission for supportive care is not necessary in patients with Klinefelter syndrome.
- Further Outpatient Care: The patient should be monitored by an endocrinologist for testosterone replacement therapy.
- Inpatient & Outpatient Medications: Administer regular testosterone injections.

Complications

1. **1.** The risk of **breast carcinoma** in men with the **XXY** variant may approach **20** times that of healthy men. **Other types of neoplasia** occur in **1.6%** of patients and include acute leukemia, Hodgkin and non-Hodgkin lymphomas, chronic myelogenous leukemia, and other myeloproliferative diseases. **Gonadal and extragonadal germ cell tumors** (mediastinal germ cell tumors, teratoma, teratocarcinoma, choriocarcinoma) may also occur.

Complications

2. Psychologic and psychiatric complications may occur in individuals with lower-than-average intelligence, hypogonadism, or impotence.

3. Vertebral collapse may result from **osteoporosis**.

4. Development of **varicose veins** and **leg ulcers** may result from venous stasis.

Complications

5. **Associated endocrine diseases** include diabetes mellitus, hypothyroidism, empty sella syndrome, hypoparathyroidism, and precocious puberty in association with human chorionic gonadotropin (hCG)-producing germ cell tumors.
6. **Benign prostatic hyperplasia** may result from testosterone supplementation. Adults undergoing such therapy should be screened for prostatic enlargement starting at age 30 years.

Complications

1. **8.** In males with polysomic X Klinefelter syndrome, the mortality rate due to cerebrovascular diseases such as aortic valvular disease and berry aneurysm rupture is more than 6 times that in healthy males aged 25-84 years. Enhanced platelet aggregation, thrombotic disease, and hypercoagulability have been demonstrated and may be related to increased estrogen levels.

Prognosis

- Early studies of men with XXY Klinefelter syndrome produced disturbing findings of an increased risk of psychiatric disturbance, criminality, and mental retardation. These results are considered highly questionable because of selection bias from institutionalized populations.
- **Babies with the XXY form differ little from healthy children.**
- **Life span is presumably normal.**

Prognosis

- Although boys with the 47,XXY karyotype may struggle through adolescence with limited academic success, many frustrations, and, in a few instances, serious emotional or behavioral difficulties, most move toward full independence from their families as they enter adulthood. Some have completed graduate education and have a normal level of functioning.

Prognosis

- Hypogonadism, low libido, and psychosocial problems can be helped by testosterone treatment.

- Gynecomastia can be corrected by mastectomy.

Pre-natal Diagnosis

- Klinefelter syndrome can be **detected prenatally** with ***amniocentesis*** and ***cytogenetic analysis of amniotic fluid***. This presents a dilemma for parents because prognosis is good but phenotypic abnormalities are possible.
- Few patients with 46,XY/47,XXY mosaicism are known to have fathered a child, which is associated with a risk of having an offspring with the 47,XXY form. All individuals with the 47,XXY form are infertile.


THANK YOU